[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN & PHARMACEUTICAL CORP.]

N-Substituted-3-oxypyridyl Betaines

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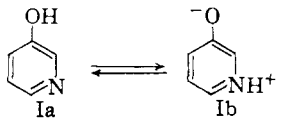
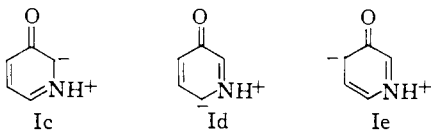
A series of N-substituted-3-oxypyridyl betaines of the type IIb and N,N'-polymethylene-bis-([3-oxypyridyl] betaines) of the type IIc have been synthesized and examined for pharmacological activity.

A convincing body of evidence, based largely on spectroscopic data,[1-5] has indicated that 3-hydroxypyridine (I) is present in aqueous solution as the neutral molecule Ia, and the dipolar ion[1] (zwitterion,[3] betaine[5]) Ib.



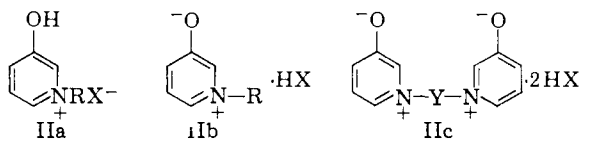
Ia Ib

The form Ib is further stabilized[3] by Ic–Ie.



Ic Id Ie

In non-aqueous solvents of decreasing dielectric constant, and with increase of temperature, the equilibrium favored is Ib → Ia.[3] This suggests that at elevated temperature reaction of 3-hydroxypyridine with an alkyl halide, RX, or a polymethylene dihalide, X–Y–X, in organic solvents such as acetonitrile or propanol should afford the quaternary salt IIa from Ia. Instead, betaines[6] (IIb and IIc) were formed.



IIa IIb IIc

A broad exploration of such betaines was indicated in view of the pharmacological significance of betaines,[7] its relevance to the biochemistry of pyridoxine,[8] and the potential of reduction to pharmacologically interesting piperidines.[9] The scope of the investigation (variation of R and Y) is indicated by the compounds IIb (Table I) and IIc (Table II)[10] which were synthesized.

The evidence for the betaine structure was based on the noted effervescence when aqueous solutions of the formed products were treated with sodium bicarbonate and precipitation of the free base of the betaine which occurred upon addition of aqueous alkali (distinction from IIa). Aqueous solutions of the products (Table I and II) gave a light orange color with ferric chloride (distinction from ethers). The picrates of the products (compounds 4 and 6, Table I) were shown to be different from the picrates of the corresponding 3-oxypyridyl ethers (see Experimental). That compound 3 (Table I) was not 2-ethyl-3-hydroxypyridine was indicated by difference in melting point of the picrates of these products.[11]

In addition, the fact that a dipicrate is readily formed with compound 1 (Table II) in spite of the proximity of the two nitrogen atoms,[12,13] indicates that such formation is not involved with protonation at the nitrogen, and supports a betaine structure.

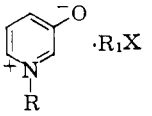
For the preparation of the compounds, the alkyl halide was refluxed with an equivalent amount of 3-hydroxypyridine in solvents such as acetonitrile or propanol. However, other solvents, including *t*-butyl alcohol, toluene, pyridine and nitropropane were serviceable. With the *n*-propyl and *n*-butyl halides the isolation of pure IIb was not effected, although the betaine was obtained using the corresponding tosylates as the alkyl reactant.

For the reaction to proceed readily it was desirable that the halides be in the primary position, although in a few cases (compounds 20, 21a, Table II) secondary halides yielded the product IIc.

While ethylene dibromide reacted to give compound 3 (Table II), a variety of other *vic*-dihalides and related structures including ethylene dichloride, ethylene diacetate, 1,2-dibromopropane, 1,2-dibromobutane, 2,3-dibromobutane, 1,2,3,4-tetrabromobutane, *cis*- and *trans*-1,2-dichloroethylene, isobutylene chlorohydrin and pentaerythritol tetrabromide failed to react and only 3-hydroxypyridine was recovered.[14] With several other *vic*-dihalides as 2,3-dichloro-*p*-dioxane[15] and 1,2-dichloroethyl

(1) D. E. Metzler and E. E. Snell, THIS JOURNAL, **77**, 2431 (1955).
(2) A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956).
(3) S. F. Mason, *ibid.*, 5010 (1957).
(4) P. Sensi and G. G. Gallo, *Ann. chim. (Rome)*, **44**, 232 (1954).
(5) W. Baker and W. D. Ollis, *Quart. Revs. (London)*, **11**, 15 (1957).
(6) Since our work was completed, papers have appeared confirming these views: (a) H. Furst and H. T. Dietz, *J. prakt. Chem.*, **4**, 147 (1956); (b) D. A. Prins, *Rec. trav. chim.*, **76**, 58 (1957); (c) K. Mecklenborg and M. Orchin, *J. Org. Chem.*, **23**, 1591 (1958).
(7) (a) E. A. Hosein and H. McLennan, *Nature*, **183**, 328 (1959); (b) R. Hunt and R. R. Renshaw, *J. Pharmacol. Exp. Therap.*, **29**, 17 (1926); (c) H. Sobotka and J. Austin, THIS JOURNAL, **73**, 3077 (1951); (d) C. R. Stephens, K. Murai, K. J. Brunings and R. B. Woodward, *ibid.*, **78**, 4155 (1956); (e) D. L. Jones, R. H. Hubble and H. J. Byrne, *Antibiotics & Chemotherapy*, **6**, 391 (1956); (f) T. C. Myers and A. L. Jibril, *J. Org. Chem.*, **22**, 180 (1957); (g) R. R. Renshaw and M. E. McGreal, THIS JOURNAL, **54**, 1471 (1932).
(8) J. B. Longnecker and E. E. Snell, *Proc. Natl. Acad. Sci. U. S.*, **42**, 221 (1956).
(9) S. L. Shapiro, K. Weinberg, T. Bazga and L. Freedman, THIS JOURNAL, **81**, 5146 (1959).
(10) The ease of isolation of the betaine salts IIc contrasts with similar reactions using pyridine instead of 3-hydroxypyridine; see R. E. Lyle and J. J. Gardikes, *ibid.*, **77**, 1291 (1955).
(11) W. Gruber, *Can. J. Chem.*, **31**, 564 (1953), reports the melting point of the picrate of 2-ethyl-3-hydroxypyridine as 173–175°.
(12) For related work involving formation of mono- or dipicrate as a function of distance between nitrogen atoms, see R. A. Abramovitch, *J. Chem. Soc.*, 3839 (1954).
(13) T. R. Harkins and H. Freiser, THIS JOURNAL, **77**, 1374 (1955).
(14) Many similar *vic*-dihalides are dehydrohalogenated with iodide ion; see J. Hine and W. H. Brader, Jr., *ibid.*, **77**, 361 (1955).
(15) P. Salomaa, *Acta Chem. Scand.*, **8**, 744 (1954).

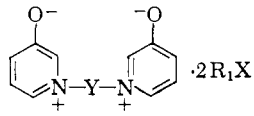
TABLE I

3-OXYPYRIDYL BETAINES  ·R_1X

No.	R	R_1X	M.p., °C.[a]	RS[b]	Yield,[c] %	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1[e]	CH_3—	HI	109–111	A	74	C_6H_8INO					5.9	5.7
2	CH_3—	HPic.[f]	201–202	B		$C_{12}H_{10}N_4O_8$	42.6	42.7	3.0	2.7		
3	C_2H_5—	HBr	99–102	B	54	$C_7H_{10}BrNO$	41.2	41.3	4.9	5.0	6.9	7.4
4	C_2H_5—	HPic.[f]	153–155	C		$C_{13}H_{12}N_4O_8$	44.3	44.2	3.4	3.5	15.9	15.7
5	n-C_3H_7—	HT[g]	129–130	D	62	$C_{15}H_{19}NO_4S$	58.3	58.0	6.1	6.3	4.5	4.7
6	n-C_3H_7—	HPic.[f]	156–157	C	61	$C_{14}H_{14}N_4O_8$	45.9	46.2	3.9	3.9	15.3	15.2
7	n-C_4H_9—	HT[g]	118–119	D	31	$C_{16}H_{21}NO_4S$	59.4	59.2	6.5	6.3	4.3	4.1
8	n-C_4H_9—	HPic.[f]	128–130	C		$C_{15}H_{16}N_4O_8$	47.4	47.3	4.2	3.9	14.7	14.8
9	CH_2=$CHCH_2$—	HBr	97–99	E	50	C_8H_8BrNO	44.4	44.4	4.6	4.9	6.5	6.6
10	CH_2=CCH_3CH_2—	HCl	139–144	E	70	$C_9H_{12}ClNO$	58.2	58.1	6.5	6.5	7.5	7.8
11	CH_2=$CClCH_2$—	HCl	153–155	E	15	$C_8H_9Cl_2NO$	46.6	47.2	4.4	4.2	6.8	7.0
12	CH_3CCl=$CHCH_2$—	HCl	181–182	D	5	$C_9H_{11}Cl_2NO$	49.1	49.1	5.0	4.8	6.4	6.2
13	C_6H_5CH=$CHCH_2$—	HCl	137–140	G	66	$C_{14}H_{14}ClNO$	67.9	68.0	5.7	5.7	5.7	5.6
14	$C_6H_5CH_2$—	HCl	154–157	G	33	$C_{12}H_{12}ClNO$					6.3	5.9
15[h]	$C_6H_5CH_2$—	HBr	125–128	F	67[i]	$C_{12}H_{12}BrNO$	54.1	54.3	4.5	4.6	5.3	5.2
16	$C_6H_5CH_2$—	H_2O	107–111	H	70	$C_{12}H_{13}NO_2$	70.9	69.8	6.5	6.2	6.9	6.9
17	4-$ClC_6H_4CH_2$—	HCl	184–185	F	75[j]	$C_{12}H_{11}Cl_2NO$	56.3	56.1	4.3	4.7	5.5	5.5
18	4-$ClC_6H_4CH_2$—	HPic.[f]	191–194	C		$C_{18}H_{14}ClN_4O_8$	48.2	48.4	2.9	3.0	12.5	12.2
19	4-$ClC_6H_4CH_2$—	CH_3I[k]	125–127	C	56	$C_{13}H_{13}ClINO$	43.2	42.9	3.6	3.5	3.9	4.3
20	$HOCH_2CH_2$—	HCl	139–144	I	70	$C_7H_{10}ClNO_2$	47.9	47.9	5.7	5.7	8.0	7.7
21	$HOCH_2CH_2$—	HBr	122–123	I	62	$C_7H_{10}BrNO_2$	38.2	38.2	4.5	4.7	6.4	6.4
22	$HOCH_2CH_2$—	...	158–159	I	29	$C_7H_9NO_2$					10.1	10.1
23[l]	n-$C_3H_7OCOCH_2$—	HCl	157–159	I	42	$C_{10}H_{14}ClNO_3$	51.8	51.3	6.0	6.3	6.0	5.7
24	n-$C_3H_7OCOCH_2$—	[m]	74–78	H	44	$C_9H_{11}NO_3$	56.3	56.0	7.1	7.1	6.6	6.3
25	$CH_3COOCH_2(CH_2)_3$—	HBr	94–96	F	57	$C_{11}H_{16}BrNO_3$	45.5	45.8	5.5	5.5		
26	BPT[n]	HBr	202–204	E	16	$C_{27}H_{38}BrNO_4$					2.7	2.8
27	BPC[o]	HBr	178–210	J		$C_{35}H_{54}BrNO_3$					2.3	2.3
28	$Cl_3C(CH_2)_4$—	HCl	175–176	K	34	$C_{10}H_{13}Cl_4NO$	39.3	39.5	4.3	4.2	4.6	5.0
29	CH_2—$CHCH_2$— 	HCl	133–135	L	11	$C_8H_{10}ClNO_2$	51.2	50.8	5.3	5.4	7.5	7.2
30[p]	$H_2N(CH_2)_2$—	2HBr	218–222	D	25	$C_7H_{12}Br_2N_2O$					9.3	9.4
31	$(CH_3)_2N(CH_2)_2$—	2HCl	238–239	D	63	$C_9H_{16}Cl_2N_2O$	45.2	45.1	6.7	6.6	11.7	11.9
32	$(CH_3)_2N(CH_2)_2$—	$2CH_3I$	167–171	D	44	$C_{11}H_{20}I_2N_2O$	29.3	29.3	4.4	4.5		
33	$(CH_3)_2N(CH_2)_3$—	2HCl	227–233	D	34	$C_{10}H_{18}Cl_2N_2O$	47.4	47.2	7.1	7.0	11.1	11.0
34	$(CH_3)_2NCH_2CHCH_3$—	2HCl	205–209	B	15	$C_{10}H_{18}Cl_2N_2O$	47.4	47.1	7.1	7.0	11.1	11.0
35	$NC(CH_2)_4$—	HBr	191–194	F	58	$C_{10}H_{13}BrN_2O$	46.7	46.9	5.1	4.9	10.9	10.9
36	$NC(CH_2)_5$—	HCl	119–121	F	58	$C_{11}H_{15}ClN_2O$	58.3	57.9	6.6	6.4	12.4	12.3
37	CH_3COCH_2—	HCl	134–136	F	48	$C_8H_{10}ClNO_2$	51.2	51.3	5.3	5.2	7.5	7.7
38	PA[q]	HCl	205–207	F	80	$C_{13}H_{12}ClNO_2$					5.6	5.8
39	4-Cl—PA[q]	HBr	231–233	N	64	$C_{13}H_{11}BrClNO_2$	47.8	47.7	3.4	3.8		
40	4-Br—PA[q]	HBr	255–257	N	50	$C_{13}H_{11}Br_2NO_2$	41.8	42.2	3.0	2.8	3.8	3.7
41	4-NO_2—PA[q]	HBr	235–237	N	70	$C_{13}H_{11}BrN_2O_4$	46.0	45.8	3.2	3.6		
42	4-C_6H_5—PA[q]	HBr	235–237	D	49	$C_{19}H_{16}BrNO_2$	61.6	61.4	4.3	4.7	3.8	3.7
43	2,4-diCH_3—PA[q]	HCl	250–252	N	77	$C_{15}H_{16}ClNO_2$	64.9	64.6	5.8	5.6	4.0	4.8
44[r]	3,4-diCH_3O—PA[q]	HCl	226–227	C	47	$C_{15}H_{16}ClNO_4$	54.9	54.3	5.5	5.2		

[a] Melting points are not corrected. [b] RS = recrystallizing solvent; A = acetone–ether; B = ethanol; C = water; D = methanol–ethyl acetate; E = ethanol–ether; F = ethanol–ethyl acetate; G = acetonitrile; H = ethyl acetate; I = ethanol–heptane; J = acetone; K = acetonitrile–methanol; L = ethyl acetate–ether; M = methanol–ether; N = methanol. [c] Yields are based on recrystallized product. [d] Analyses by Weiler and Strauss, Oxford, England. [e] Does not depress the melting point of the product prepared as described by S. A. Harris, T. J. Webb and K. Folkers, THIS JOURNAL, **62**, 3198 (1940). [f] HPic. = picric acid. [g] HT = *p*-toluenesulfonic acid. [h] Reported, H. M. Wuest and E. H. Sakal, THIS JOURNAL, **73**, 1214 (1951), m.p. 133–136°, characterized as the quaternary salt. [i] When the solvent was varied the following crude yields were obtained: *t*-Butyl alcohol, 83%; acetonitrile, 83%; isopropyl alcohol–toluene, 82%; nitropropane, 49%; toluene, 92%. [j] Variation of solvent gave the following crude yields: *t*-butyl alcohol, 84%; acetonitrile, 90%; isopropyl alcohol–toluene, 68%; toluene, 69%; pyridine, 56%. [k] Although not proved, the structure is probably the *p*-chlorobenzyl iodide quaternary of 3-methoxypyridine. [l] The initial reactant, ethyl chloroacetate, was transesterified in the 1-propanol medium. [m] Crystallizes with 0.5 mole of water which has not been included in the formula. [n] The initial reactant was testosterone β-bromopropionate; S. L. Shapiro, K. Weinberg and L. Freedman, *J. Org. Chem.*, 21, 1300 (1956). [o] The initial reactant with cholesteryl β-bromopropionate (see Experimental). [p] Br calcd./found: 53.3/51.3. [q] PA = phenacyl. [r] Analyses calculated on monohydrate.

TABLE II

BIS-3-OXYPYRIDYL BETAINES  ·2R₁X

No.	Y	2R₁X	M.p., °C.[a]	RS[b]	Yield,[c] %	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1[e]	$-CH_2-$	HI	205–208	C	39							
2	$-CH_2-$	HPic.[f]	239	C		$C_{23}H_{16}N_8O_{16}$	41.8	42.3	2.4	2.5	17.0	16.7
3	$-(CH_2)_2-$	HBr	295–296	D	10	$C_{12}H_{14}Br_2N_2O_2$	38.1	37.9	3.7	3.7	7.4	7.3
4	$-(CH_2)_2-$	HT[g]	290–292	P	9	$C_{26}H_{28}N_2O_8S_2$					5.0	4.7
5	$-(CH_2)_3-$	HCl	226–227	N	24	$C_{13}H_{16}Cl_2N_2O_2$	51.5	51.3	5.3	5.5	9.2	8.9
6	$-(CH_2)_3-$	HBr[h]	253–258	O	17	$C_{13}H_{15}BrN_2O_2$	50.2	50.5	4.8	4.9	9.0	9.1
7	$-(CH_2)_3-$	HBr	211–213	K	19	$C_{13}H_{16}Br_2N_2O_2$	40.0	39.9	4.1	4.4	7.1	6.7
8	$-(CH_2)_3-$	CH_3I	212–215	D	43	$C_{15}H_{20}I_2N_2O_2$	35.0	35.2	3.9	4.0		
9	$-(CH_2)_3-$	C_2H_5I	160–163	F	48	$C_{17}H_{24}I_2N_2O_2$	37.6	37.4	4.4	4.3	5.2	5.1
10	$-CH_2-C(CH_2)-$	HCl	279	Q	3	$C_{13}H_{14}Cl_2N_2O_2$	51.8	52.1	4.7	4.7	9.3	8.8
11	$-(CH_2)_4-$	HCl	267–269	D	39	$C_{14}H_{18}Cl_2N_2O_2$					8.8	8.8
12	$-(CH_2)_4-$	H_2O	195–198	I	50	$C_{14}H_{20}N_2O_3$	60.0	60.6	7.1	7.2		
13	$-(CH_2)_4-$	HPic.[f]	224–226	C	63	$C_{26}H_{22}N_8O_{16}$	44.4	44.1	3.1	3.4	16.0	15.7
14	$-(CH_2)_4-$	CH_3I	194–198	D	46	$C_{16}H_{22}I_2N_2O_2$	36.4	36.5	4.2	4.3		
15	$-(CH_2)_4-$	C_2H_5I	166–167	D	57	$C_{18}H_{26}I_2N_2O_2$	38.9	38.8	4.7	4.8	5.0	4.8
16	$-CH_2CH=CHCH_2-$	HBr	220–222	N	72	$C_{14}H_{16}Br_2N_2O_2$	41.6	41.8	4.0	4.2	6.9	7.4
17	$-(CH_2)_5-$	HCl	217–218	D	52	$C_{15}H_{20}Cl_2N_2O_2$	54.4	54.1	6.0	6.2	8.5	8.1
18	$-(CH_2)_5-$	HBr	231–233	O	74	$C_{15}H_{20}Br_2N_2O_2$	42.9	42.8	4.8	5.0	6.7	6.9
19	$-(CH_2)_5-$	CH_3I	156–159	D	58	$C_{17}H_{24}I_2N_2O_2$	37.6	37.6	4.4	4.6	5.2	5.2
20	$-(CH_2)_3CHCH_3-$	HBr	203–206	F	27	$C_{15}H_{20}Br_2N_2O_2$	42.9	43.1	4.8	4.8	6.7	7.0
21	$-(CH_2)_6-$	HBr	274–275	P	66	$C_{16}H_{22}Br_2N_2O_2$	44.2	44.4	5.1	5.3	6.5	6.9
21a	$-CHCH_3(CH_2)_2CHCH_3-$	HBr	247–249	D	12	$C_{16}H_{22}Br_2N_2O_2$	44.2	44.7	5.1	5.5	6.5	6.5
22	$-(CH_2)_9-$	HBr	227–231	F	9	$C_{19}H_{28}Br_2N_2O_2$	47.9	47.2	5.9	5.7	5.9	5.7
23	$-(CH_2)_{10}-$	HBr	176–178	F	72	$C_{20}H_{30}Br_2N_2O_2$	49.0	49.3	6.1	6.2	5.7	5.8
24	1,2-$CH_2C_6H_4CH_2-$	HBr	252–255	D	31	$C_{18}H_{18}Br_2N_2O_2$					6.2	5.9
25	1,3-$CH_2C_6H_4CH_2-$	HBr	274–286	D	68	$C_{18}H_{18}Br_2N_2O_2$	47.6	47.9	4.0	4.1	6.2	5.8
26	1,4-$CH_2C_6H_4CH_2-$	HBr	277–280	D	88	$C_{18}H_{18}Br_2N_2O_2$	47.6	47.9	4.0	3.8	6.2	5.8
27	1,4-$CH_2C_6H_4CH_2-$	CH_3I	203–204	D	34	$C_{20}H_{22}I_2N_2O_2$	41.7	41.6	3.8	4.3	4.9	4.8
28	$-CH_2COCH_2-$	HCl	>300	D	3	$C_{13}H_{14}Cl_2N_2O_3$	49.2	48.7	4.4	4.5	8.8	8.9
29	$-CH_2OCH_2-$	HCl	211–213	D	55	$C_{12}H_{14}Cl_2N_2O_3$	47.2	47.2	4.6	4.9		
30	$-CH_2OCH_2-$	HPic.[f]	236	C		$C_{24}H_{20}N_8O_{17}$	41.7	41.9	2.9	3.0	16.2	16.0
31	$-(CH_2)_2O(CH_2)_2-$	HCl	169–172	F	16	$C_{14}H_{18}Cl_2N_2O_2$	50.5	49.8	5.4	5.2	8.4	8.1

[a,c,d,f,g] Same significance as in Table I. [b] Same significance as in Table I; additional solvent systems employed: O = ethanol-water; P = methanol-water; Q = ethanol-acetone. [e] Not obtained analytically pure, reflecting loss of hydrogen iodide. [h] Monohydrobromide.

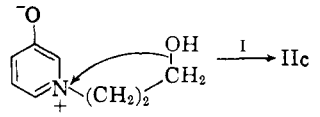
ethyl ether, dehydrohalogenation occurred and the hydrochloride of the reactant 3-hydroxypyridine was isolated. Dehydrohalogenation also occurred with benzhydryl bromide and cyclopentyl bromide.

The reaction with 2,3-dichloropropene-1 was of particular interest in that it afforded a monobetaine (compound 11, Table I), characterized as the reaction product with the allylic chloride, and the bis-betaine (compound 10, Table II) which indicated reaction as well with the vinyl chloride.

Comparison of bromides and chlorides as the reactant halide showed that the *n*-propyl chloride or *n*-butyl chloride failed to react, while the corresponding bromides afforded the betaine, characterized as the picrate. In comparable runs wherein chlorides and bromides were evaluated, the bromides as a rule gave somewhat better yields (compounds 14, 15; 20, 21 of Table I; 5, 6; 17, 18 of Table II).

When the reactant halide had an additional functional group, as, for example, an ω-halo group, the bis-betaines IIc were formed, and were isolable as the dihydrohalides. Of interest was the fact that both the monohydrobromide and the dihydrobromide (compounds 6 and 7, Table II) were isolated in the reaction with trimethylene bromide. When trimethylene chlorobromide or tetramethylene chlorobromide was used, the betaine isolated in each instance was the dihydrobromide. A similar pattern prevailed when hydroxy or acetoxy were the other ω-functional groups of three or four carbon reactant halides. Although ethylene chlorohydrin and ethylene bromohydrin gave the expected compounds (20, 21, Table I), when longer chains separated the functional groups, as ω-bromobutyl acetate, the anticipated monobetaine (compound 25, Table I) was obtained, as well as N,N′-tetramethylene-bis-(3-oxypyridyl betaine) dihydrobromide. In turn, 3-bromopropanol did not give any of the monobetaine and afforded as the only isolable product N,N′-trimethylene-bis-(3-oxypyridyl betaine) dihydrobromide.

These observations may be explained by forms shown[16,17]



The isolation of the dihydrobromide of IIc is probably a function of its superior crystallizability over mixed salts which theoretically might be realized.

Other functional groups on the reactant halides such as trichloromethyl, oxiranyl, amino, dialkylamino, cyano, acetyl and phenacyl did not interfere with the normal course of the reaction.

For the reaction with β, γ-epoxypropyl chloride (preparation of compound 29, Table I) it is not established whether the reaction proceeds through attack at the chlorine-bearing carbon, or by opening of the oxide ring followed by dehydrohalogenation.[18]

When ethyl chloroacetate[19] was the reactant halide in the propanol medium, transesterification[20] to N-(carbopropoxymethyl)-3-oxypyridyl betaine hydrochloride was observed.

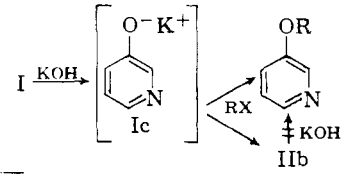
In the attempt to extend the reaction to the preparation of the bis-betaine from ethyl dichloroacetate, no product was isolated, and the reaction likewise failed with a variety of aminoalcohol esters of dichloroacetic acid.

The failure of these reactions may be rationalized on the basis of the decreased reactivity of methylene dihalides,[21] although with methylene diiodide the expected product was obtained (compound 1, Table II).

While the bis-betaine was readily obtained with α,α'-dichloromethyl ether, the reaction in a solvent failed with the less reactive[22] β,β'-dichloroethyl ether, as well as with the presumably more reactive β,β'-diiodoethyl ether. However, employment of β,β'-dichloroethyl ether as the solvent gave the required compound (compound 31, Table II).

Striking indication of the driving force for betaine formation is evident in that even condensation under conditions wherein high concentrations of potassium hydroxide were present, the betaine as well as the 3-alkoxypyridyl ether were formed (Scheme I).

SCHEME I. BETAINE FORMATION IN KOH MEDIUM



(16) S. Oae, THIS JOURNAL, **78**, 4030, 4032, 4034 (1956).

(17) P. R. Wright and W. E. McEwen, *ibid.*, **76**, 4540 (1954).

(18) (a) Y. M. Beasley, V. Petrow and O. Stephenson, *J. Pharm. Pharmacol.*, **10**, 47 (1958); (b) A. W. Adams, E. G. E. Hawkins, G. F. Oldham and R. D. Thompson, *J. Chem. Soc.*, 559 (1959).

(19) H. Bojarska-Dahlig and T. Urbański, *C. A.*, **48**, 1337 (1954), noted failure of chloroacetic acid to react with 3-hydroxypyridine.

(20) E. C. Schreiber and E. I. Becker, THIS JOURNAL, **72**, 4829 (1950).

(21) J. Hine, C. H. Thomas and S. J. Ehrenson, *ibid.*, **77**, 3886 (1955).

(22) F. B. Tutwiler and R. L. McKee, *ibid.*, **76**, 6342 (1954).

In the instances wherein R was ethyl and *n*-propyl, the ether and betaine were both characterized, while R as *p*-chlorobenzyl afforded only the betaine IIb, with no ether being isolated. Moreover, treatment of the betaines with strong alkali does not convert them to the 3-alkoxy ethers.

When the betaine hydrohalide salts were neutralized the free betaines could be isolated. These compounds were characterized in varying degrees of hydration (compounds 16, 22, Table I; compound 12, Table II) and were quite hygroscopic and discolored (red) on exposure to air. The betaines in turn could be alkylated to yield 3-alkoxypyridine quaternaries.

The synthetic work was extended to pyridoxine, and the corresponding bis-betaines from 1,6-dibromohexane, 1,4-dibromobutene-2 and bis-(chloromethyl) ether were readily prepared.

Pharmacology.—Many of the compounds were screened for a variety of pharmacological effects.[23] No regularity in pattern was observed other than the uniform freedom from toxicity, particularly of the betaines of Tables I and II. Most of these compounds showed no toxicity at levels of 1,000 mg./kg. A variety of positive responses[24] was noted: antihistamine activity (Table I, compounds 10, 13, 25), potentiation of histamine (Table I, compound 43), hypotension (Table I, compounds 32, 34), anticonvulsant activity (Table I, compound 30; Table II, compound 21), potentiation of Evipal sleeping time (Table I, compound 31), inhibition of adrenalin (Table I, compound 41; Table II, compounds 18, 19), potentiation of adrenalin (Table I, compounds 32, 40, 43), anti-inflammatory activity (Table I, compounds 39, 41, 43; Table II, compound 14). The results of the antibacterial screening will be reported at a later date.

Experimental[25]

Materials.—The halide reactants were all commercially available unless otherwise specified and were used without further purification.

N-Methyl-3-oxypyridyl Betaine Hydriodide (Table I, Compound 1).—A mixture of 9.5 g. (0.1 mole) of 3-hydroxypyridine and 14.2 g. (0.1 mole) of methyl iodide in 50 ml. of 1-propanol was heated under reflux for 8 hours. After removal of the propanol there was obtained 23 g. of crude product which was recrystallized (acetone–ether) to afford 17 g. of the product.

The compound did not depress the melting point of 3-hydroxypyridine methiodide,[26] m.p. 108–110°, mixed m.p. 109–111°.

The aqueous solution of the compound effervesced on addition of sodium bicarbonate solution. The melting

(23) Ultraviolet absorption studies, S. L. Shapiro, K. Weinberg and L. Freedman (in preparation) indicate that in aqueous solutions the compounds are present as an equilibrium mixture of the cation IIa, and the dipolar ion IIb, IIc. The pharmacological implications of this equilibrium will be therein discussed.

(24) For the methods used in screening see: (a) S. L. Shapiro, H. Soloway and L. Freedman, *J. Am. Pharm. Assoc. (Sci. Ed.)*, **46**, 333 (1957), for antihistamine and anti-inflammatory activity; (b) S. L. Shapiro, H. Soloway and L. Freedman, THIS JOURNAL, **80**, 2743 (1958), for blood pressure; (c) S. L. Shapiro, I. M. Rose, E. Roskin and L. Freedman, *ibid.*, **80**, 1648 (1958), for anticonvulsant effect and Evipal sleeping time; (d) S. L. Shapiro, H. Soloway, E. Chodos and L. Freedman, *ibid.*, **81**, 386 (1959), for effect on adrenalin.

(25) Descriptive data shown in the tables are not reproduced in the Experimental section. In this section, typical procedures are described.

(26) S. A. Harris, T. J. Webb and K. Folkers, THIS JOURNAL, **62**, 3198 (1940), report m.p. 114–116°.

point of the picrate of that compound, 199.5–201°, did not depress the melting point of compound 2 (Table I), mixed m.p. 201–202°

3-Ethoxypyridine was prepared as previously described,[27] b.p. 78–81° (15 mm.), and was converted to the hydrochloride with methanolic hydrogen chloride, m.p. 165–167°.

Anal. Calcd. for $C_7H_{10}ClNO$: C, 52.7; H, 6.3; N, 8.8. Found: C, 52.7; H, 6.2; N, 9.2.

The picrate melted at 122–124° (water) (see Table I, compound 4).

N-*n*-Propyl-3-oxypyridyl Betaine Picrate (Table I, Compound 6). **Attempted Preparation of the Hydrobromide.**—A mixture of 9.5 g. (0.1 mole) of 3-hydroxypyridine and 12.3 g. (0.1 mole) of *n*-propyl bromide in 50 ml. of 1-propanol was heated under reflux for 20 hours. After removal of the propanol, the oily residue could not be crystallized. A small portion was converted to the product by treatment with aqueous picric acid.

***N*-*n*-Propyl-3-oxypyridyl Betaine *p*-Toluenesulfonate** (Table I, Compound 5).—A mixture of 4.75 g. (0.05 mole) of 3-hydroxypyridine and 10.7 g. (0.05 mole) of *n*-propyl *p*-toluenesulfonate in 25 ml. of acetonitrile was heated under reflux. After removal of 10 ml. of acetonitrile, the product crystallized (11.3 g.), m.p. 127–128°.

Its picrate melted at 156–157° (water) and did not depress the melting point of compound 6 (Table I), mixed m.p. 156–157°.

3-*n*-Propoxypyridine Hydrochloride.—A mixture of 9.5 g. (0.1 mole) of 3-hydroxypyridine in 100 ml. of 1-propanol was treated with 6.1 g. of powdered potassium hydroxide. The formed water was removed by distillation and 12.3 g. (0.1 mole) of *n*-propyl bromide added. The reaction mixture was heated at 75° for 10 minutes and the formed potassium bromide, 8.0 g. (67%), separated. The filtrate was acidified with dilute sulfuric acid and the solvents removed *in vacuo*. The residue was treated with 50 ml. of 6 *N* sodium hydroxide and the two-phase system so obtained was steam distilled. The distillate (250 ml.) was extracted with three 100-ml. portions of ether, the ether evaporated, and the residual oil treated with methanolic hydrogen chloride. Upon addition of ether, 0.5 g. (3%) of product separated, m.p. 117–119°, and was recrystallized (methanol–ethyl acetate), m.p. 118–120°.

Anal. Calcd. for $C_8H_{17}ClNO$: N, 7.8. Found: N, 7.8.

The picrate melted 100–102° (water).

Anal. Calcd. for $C_{14}H_{14}N_4O_8$: C, 45.9; H, 3.8; N, 15.3. Found: C, 46.3; H, 4.0; N, 15.0.

The residue from the steam distillation was neutralized and upon treatment with aqueous picric acid afforded the picrate, m.p. 149–152° (water), which did not depress the m.p. of compound 6 (Table I), mixed m.p. 150–153°.

When *p*-chlorobenzyl chloride was substituted for the *n*-propyl bromide under similar reaction conditions, no (3-*p*-chlorobenzyloxy)-pyridine was obtained in the steam distillate. The pot residue, upon neutralization and treatment with picric acid as above, gave the picrate of N-*p*-chlorobenzyl-3-oxypyridyl betaine (compound 18, Table I), m.p. 191–194° (water), mixed m.p. 191–194°.

A similar reaction with benzhydryl chloride yielded none of the corresponding ether in the steam distillate, and neutralization of the pot residue and treatment with aqueous picric acid afforded only the picrate of 3-hydroxypyridine, m.p. 190–193° (water), not depressing with the authentic picrate of 3-hydroxypyridine, m.p. 196–198°, mixed m.p. 196–197°.

When strongly alkalinized aqueous suspensions of compounds 1, 3 and 17 (Table I) were subjected to steam distillation, there was no evidence of the 3-alkoxypyridine in the distillate.

N,N′-([1-Methylidine]-ethylene)bis-3-oxypyridyl Betaine Dihydrochloride (Table II, Compound 10).—A mixture of 9.5 g. (0.1 mole) of 3-hydroxypyridine and 5.6 g. (0.05 mole) of 2,3-dichloropropene-1 in 50 ml. of 1-propanol was heated under reflux for 20 hours. When cool, an initial crop of crystals was separated (1.5 g.) and then a second fraction of 2.45 g. The initial crop was recrystallized (ethanol–acetone) to yield the product (0.6 g.).

The second crop, upon recrystallization, gave N-(2-chloroallyl)-3-oxypyridyl betaine hydrochloride (compound 11, Table I), 1.5 g. (15%). The structural assignment was made on the basis that the chlorine atom in the allylic position at carbon-3 of the reactant 2,3-dichloropropene-1 was considerably more reactive than the vinyl chloride at carbon-2.

N-(Benzyl)-3-oxypyridyl Betaine Monohydrate (Table I, Compound 16).—A solution of 2.66 g. (0.01 mole) of compound 15 (Table I) in 15 ml. of 1-propanol and 4 ml. of methanol was treated with a solution of 0.23 g. (0.01 g. atom) of sodium in 5 ml. of methanol and 5 ml. of 1-propanol. The methanol was removed and the formed sodium bromide (0.79 g.) separated. The filtrate was evaporated to dryness and the residue, which crystallized on standing, gave 1.3 g. Upon recrystallization the formed crystals reddened under the influence of air.

The free base so obtained gave an analysis which reflected one mole of water. In general, throughout this work it was difficult to obtain analytically pure products from the betaine salts. The formed free bases appeared to contain variable amounts of water.

3-Methoxypyridine-*p*-chlorobenzyl Iodide (Table I, Compound 19).—N-(*p*-Chlorobenzyl)-3-oxypyridyl betaine hydrochloride (compound 17, Table I) was converted to the crude free base by treating 6.4 g. in 10 ml. of water with a solution of 1.1 g. of sodium hydroxide in 5 ml. of water. After standing several hours, the crude free base (5.2 g.), m.p. 119–123°, separated. It could not be obtained analytically pure.

A solution of 0.5 g. of the free base in 6 ml. of acetonitrile and 2 ml. of methyl iodide was heated under reflux for 4 hours. An additional 2 ml. of methyl iodide was added and the reaction mixture stored at 20° for 20 hours. The solvents were evaporated and the residue crystallized to yield 0.6 g. which on recrystallization (water) afforded yellow crystals of the product, m.p. 125–127°. The yellow color of the product was not removed by treatment with sodium bisulfite.

N-(Carbopropoxymethyl)-3-oxypyridyl Betaine Hydrochloride (Table I, Compound 23).—A mixture of 9.5 g. (0.1 mole) of 3-hydroxypyridine and 12.2 g. (0.1 mole) of ethyl chloroacetate in 60 ml. of 1-propanol was heated under reflux for 24 hours. When cool, 25 ml. of solvent was removed and the crystalline product, 15 g. (69%), separated. Upon recrystallization the analyses indicated that transesterification[20] with the solvent 1-propanol had occurred.

N-(ω-Acetoxybutyl)-3-oxypyridyl Betaine Hydrobromide (Table I, Compound 25).—A mixture of 9.5 g. (0.1 mole) of 3-hydroxypyridine and 19.3 g. of ω-bromobutyl acetate in 50 ml. of acetonitrile was heated under reflux for 8 hours. After standing overnight, 1.5 g. of crystalline material separated which on recrystallization (methanol) gave 0.5 g., m.p. 261–262°. This proved to be the dihydrobromide of N,N′-tetramethylene-bis(3-oxypyridyl) betaine.

Anal. Calcd. for $C_{14}H_{18}Br_2N_2O_2$: C, 41.4; H, 4.4; N, 6.9. Found: C, 41.8; H, 4.7; N, 6.6.

The filtrate was evaporated to dryness, and the residue granulated under ethyl acetate gave 22.5 g. which was recrystallized to give 16.5 g. of product.

A similar reaction with tetramethylene chlorobromide also yielded the dihydrobromide of N,N′-tetramethylene bis-(3-oxypyridyl) betaine, m.p. 261–263°, mixed m.p. 261–262°.

Cholesteryl β-Bromopropionate.—A solution of 9 ml. of β-bromo-propionyl chloride in 120 ml. of toluene was cooled to −10° and treated dropwise over 2 hours with continued stirring and cooling with a solution of 5 g. of cholesterol in 150 ml. of toluene and 10 ml. of pyridine. Stirring was continued for 20 hours at 20°. The reaction mixture was washed successively with water, dilute hydrochloric acid, dilute sodium bicarbonate and water. The separated toluene layer was dried (magnesium sulfate), filtered and the toluene removed. The residue when recrystallized (ethanol) gave 5 g. (80%) of product, m.p. 100–101°.

Anal. Calcd. for $C_{30}H_{49}BrO_2$: C, 69.1; H, 9.4. Found: C, 69.0; H, 8.9.

N-(Dimethylaminoethyl)-3-oxypyridyl Betaine Dihydrochloride (Table I, Compound 31).—A mixture of 9.5 g. (0.1 mole) of 3-hydroxypyridine and 14.3 g. (0.1 mole) of dimethylaminoethyl chloride hydrochloride in 60 ml. of 1-propanol was heated under reflux for 5 hours. Upon storage for 16 hours at 20°, 20 g. of crude product separated.

N,N′-Trimethylene-bis-(3-oxypyridyl) betaine Monohydrobromide and Dihydrobromide (Table II, Compounds 6

(27) H. J. den Hertog, C. Jouiversma, A. A. van der Wal and E. C. C. Willebrands-Schogt, *Rec. trav. chim.*, **68**, 275 (1949).

and 7).—A mixture of 9.5 g. (0.1 mole) of 3-hydroxypyridine and 10.1 g. (0.05 mole) of trimethylene bromide was heated under reflux for 2 hours. On cooling, 6.8 g. of crystalline precipitate formed which after recrystallization proved to be compound 6.

The filtrate concentrated to a sirup was treated with 60 ml. of acetonitrile, then with 40 ml. of methanol and filtered (carbon). The filtrate upon treatment with 100 ml. of ethyl acetate afforded compound 7.

Compound 7 was also obtained using trimethylene chlorobromide, or 3-bromopropanol as the initial reactants.

N,N'-(1,4-Butene-2-ylene)-bis-(3-oxypyridyl) betaine Dihydrobromide (Table II, Compound 16).—When a solution of 9.5 g. (0.1 mole) of 3-hydroxypyridine in 50 ml. of acetonitrile was treated with 10.7 g. (0.05 mole) of 1,4-dibromobutene-2, an immediate reaction occurred and 16.95 g. of crude product was obtained.

N,N'-(1,5[3-Oxapentylene])-bis-(3-oxypyridyl) betaine Dihydrochloride (Table II, Compound 31).—A solution of 9.5 g. (0.1 mole) of 3-hydroxypyridine in 30 ml. of β,β'-dichloroethyl ether at 100° was heated rapidly and a two-phase system resulted when the reaction mixture attained 165°. Heating was continued for 2 minutes at 180°. When cool, the supernatant liquid was decanted and the oily residue successively stirred with toluene, benzene, ether and acetone, and then dried *in vacuo* for 90 hours when crystallization occurred. Treatment with acetone–ethanol yielded 4 g. of brown crystals.

Under the usual reaction conditions, in 1-propanol no crystalline product was obtained. Under similar conditions using β,β'-diiodoethyl ether[28] and acetonitrile as the solvents the reaction failed to give a crystalline product.

Reaction of 3-Hydroxypyridine with *vic*-Dihalides and Related Compounds.—Reaction of 3-hydroxypyridine with ethylene glycol ditosylate[29] gave compound 4 (Table II). The dihydrobromide salt (compound 3, Table II) was obtainable using one or two equivalents of ethylene bromide. When ethylene chloride or ethylene diacetate was used, only 3-hydroxypyridine was isolated. The following *vic*-dihalides failed to react (3-hydroxypyridine being isolated): 1,2-dibromopropane, 1,2-dibromobutane, 2,3-dibromobutane, 1,2,3,4-tetrabromobutane, *cis*- and *trans*-1,2-dichloroethylene as well as isobutylene chlorohydrin and penta-erythritol tetrabromide.

In this category, dehydrohalogenation was noted with 2,3-dichloro-*p*-dioxane and 1,2-dichloroethyl ethyl ether to afford the hydrochloride of 3-hydroxypyridine,[30] m.p. 105–107° (ethyl acetate).

Anal. Calcd. for C_5H_6ClNO: C, 46.0; H, 4.3. Found: C, 45.8; H, 4.6.

Reaction of Methyl Dichloroacetate with 3-Hydroxypyridine.—The reaction failed using 1-propanol, acetonitrile or toluene as the solvent, and 3-hydroxypyridine was isolated.

(β-[4-Morpholino]-ethyl)-dichloroacetate Hydrochloride.—A solution of 14.7 g. (0.1 mole) of dichloroacetyl chloride in 100 ml. of benzene was treated dropwise with continual stirring over 30 minutes with a solution of hydroxyethylmorpholine in 30 ml. of benzene. There was obtained 22 g. (80%) of product which was recrystallized (ethanol–hexane) and melted at 145–147°.

Anal. Calcd. for $C_{18}H_{14}Cl_3NO_3$: N, 5.0. Found: N, 5.4.

In a similar manner there was obtained (β-diethylamino)-ethyl dichloroacetate hydrochloride, m.p. 70–75° (ethyl acetate–ether).

Anal. Calcd. for $C_{18}H_{16}Cl_3NO_2$: N, 5.3; Found: N, 5.4.

In a similar manner there was obtained (β-dimethylamino)-ethyl dichloroacetate hydrochloride, m.p. 134–136° (ethyl acetate–hexane).

Anal. Calcd. for $C_{16}H_{12}Cl_3NO_2$: N, 5.9. Found: N, 5.7.

Reaction of the title compound with 3-hydroxypyridine in acetonitrile afforded only a black oily residue.

Isolation of Uncrystallizable Oils.—In a variety of cases, the reaction product with the halide and 3-hydroxypyridine could not be crystallized. Some of these products were characterized as their picrates. Thus, propyl and butyl bromide afforded an oil which yielded compounds 6 and 8 (Table I), respectively; whereas use of the corresponding chlorides gave 3-hydroxypyridine. The picrate of N-(3-methylpentyl)-3-oxypyridyl betaine, m.p. 111–113° (water), was obtained from the oily reaction product with 1-bromo-3-methylpentane.

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.0; H, 4.9; N, 13.7. Found: C, 49.7; H, 4.8; N, 14.1.

Similarly, from crotyl bromide there was obtained the picrate of N-(crotyl)-3-oxypyridyl betaine, m.p. 111–113° (water).

Anal. Calcd. for $C_{15}H_{14}N_4O_8$: C, 47.6; H, 3.7; N, 14.8. Found: C, 47.8; H, 3.6; N, 14.8.

Oils obtained with 2,4-dibromopentane, γ,γ'-dichlorodipropyl ether and 1,7-dichloro-4-heptanone were not further characterized.

Dehydrohalogenizations.—Reactions with benzhydryl bromide and cyclopentyl bromide afforded as the only isolable product the hydrobromide of 3-hydroxypyridine, m.p. 133–135° (ethyl acetate–ether).

Anal. Calcd. for C_5H_6BrNO: N, 8.0. Found: N, 7.8.

This was converted to the free base, and did not depress the melting point of 3-hydroxypyridine, mixed m.p. 124–126°.

N,N'-Oxydimethylene-bis-([4,5-dihydroxymethyl-2-methyl-3-oxypyridyl] betaine) Dihydrochloride.—A mixture of 1.7 g. (0.01 mole) of pyridoxine and 0.56 g. (0.005 mole) of bis-(chloromethyl) ether in 140 ml. of acetonitrile was heated under reflux for 0.5 hour. When cool, the formed crystals (1.75 g., m.p. 165–180°) were separated and twice recrystallized (methanol–ethyl acetate) to give 0.22 g. (10%) of product, m.p. 197–199°.

Anal. Calcd. for $C_{18}H_{26}Cl_2N_2O_7$: C, 47.7; H, 5.7; N, 6.2. Found: C, 47.8; H, 6.4; N, 6.1.

N,N'-Hexamethylene-bis-([4,5-dihydroxymethyl-2-methyl-3-oxypyridyl] betaine) Dihydrobromide.—A mixture of 1.7 g. (0.01 mole) of pyridoxine and 1.22 g. (0.005 mole) of 1,6-dibromohexane in 10 ml. of methyl Cellosolve was heated under reflux for 1 hour. The solvent was removed and the oily residue upon granulation with ether and ethyl acetate yielded 2.0 g. of solid which was recrystallized (methanol–ethyl acetate) to give 0.55 g. (19%) of product, m.p. 176–178°.

Anal. Calcd. for $C_{22}H_{34}Br_2N_2O_6$: C, 45.4; H, 5.8; N, 4.8. Found: C, 45.5; H, 6.3; N, 4.8.

N,N'-(1,4-Buten-2-ylene)-bis-([4,5-dihydroxymethyl-2-methyl-3-oxypyridyl] betaine) Dihydrobromide.—A mixture of 1.7 g. (0.01 mole) of pyridoxine and 1.07 g. (0.05 mole) of 1,4-dibromobutene-2 in 140 ml. of acetonitrile was heated under reflux for 25 minutes. When cool, 1.35 g. (49%) of product was obtained, m.p. >300°. The analytical sample was recrystallized (methanol–acetonitrile), m.p. >300°.

Anal. Calcd. for $C_{20}H_{28}Br_2N_2O_6$: C, 43.5; H, 5.1; N, 5.1; Br, 29.0. Found: C, 43.6; H, 5.8; N, 4.8; Br, 28.6.

Similar reactions with pyridoxine and *p*-chlorobenzyl chloride and phenacyl chloride resulted in dehydrohalogenation with isolation of pyridoxine hydrochloride.

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YONKERS 1, N. Y.

(28) C. S. Gibson and J. D. A. Johnson, *J. Chem. Soc.*, 2525 (1930).

(29) C. L. Butler, W. L. Nelson, A. G. Renfrew and L. H. Cretcher, THIS JOURNAL, **57**, 575 (1935).

(30) Ref. 19 reports m.p. 204–205°.